



# Ketorolac Use Shortens Hospital Length of Stay After Bariatric Surgery: a Single-Center 5-Year Experience

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## Abstract

**Introduction** There has been a recent increased interest in the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac for post-operative pain management to minimize opioid use and decrease hospital length of stay (LOS). Although NSAID use has been controversial following bariatric surgery due to anecdotal concerns for increased gastric bleeding, the impact of ketorolac as an adjunct to opioids needs further investigation on LOS and post-operative complications like bleeding.

**Objective** This study aims to evaluate the impact of post-operative ketorolac use on opioid consumption, LOS, and bleeding risk after bariatric surgery.

**Methods** We retrospectively analyzed a prospectively maintained database of all bariatric surgery patients who either underwent sleeve gastrectomy (SG) or Roux-en-Y gastric bypass surgery (RYGB) at a tertiary center between 2011 and 2015. Patients were stratified into 2 groups based on post-operative pain control regimen as follows: (1) ketorolac and opioids and (2) opioids alone.

**Results** A total of 1555 patients were identified who underwent either SG ( $n = 1255$ ) or RYGB ( $n = 300$ ). The overall LOS was  $1.81 \pm .059$  days for ketorolac-opioid patients vs.  $2.09 \pm .065$  days for opioid-only patients ( $P < 0.001$ ). Furthermore, the risk of post-operative bleeding was similar between the two groups ( $P = 0.097$ ).

**Conclusion** Patients who received ketorolac as an adjunct to opioids had a significantly shorter LOS compared to opioid-only patients. Additionally, ketorolac use was not associated with increased risk of post-operative bleeding complications. Therefore, if not contraindicated, ketorolac should be considered routinely for post-operative pain control among bariatric surgery patients.

**Keywords** Bariatric surgery · Ketorolac · Opioids · Length of stay · Bleeding

## Introduction

Opioids have traditionally been one of the primary methods for achieving post-operative pain control. However, recently there has been an increased interest in the use of non-steroidal anti-inflammatory drugs (NSAIDs), specifically ketorolac, as an adjunct to opioids in hopes of reducing opioid consumption, minimizing post-operative side effects, and shortening hospital length of stay (LOS) [1–4]. Accordingly, ketorolac is commonly used in general surgery and other surgical

sub-specialties, as it is considered to be equivalent to opioids in relieving pain without many of the undesirable side effects attributed to opioids such as nausea, vomiting, constipation, and drowsiness [4–12]. At the same time, gastrointestinal bleeding, which is considered to be the single greatest post-operative side effect of ketorolac use, has fueled concerns and a debate as to whether it can be safely administered in the post-operative setting.

While previous studies have compared ketorolac use with opioids with respect to analgesic potency, side effects, LOS, and bleeding rates after surgery, there is a paucity of literature on the post-operative effects of ketorolac following bariatric surgery [3, 4, 13–15]. The purpose of this paper is to expand upon the current literature by evaluating the impact of post-operative ketorolac use with regard to minimizing opioid consumption, post-operative LOS, and occurrence of bleeding after bariatric surgery.

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## Materials and Methods

### Study Population

All research was conducted with Institutional Review Board approval. We retrospectively analyzed a prospectively maintained database of 1555 obese patients who underwent either sleeve gastrectomy (SG) or Roux-en-Y gastric bypass surgery (RYGB) at a tertiary academic center between 2011 and 2015.

### Patient Inclusion and Exclusion

All patients  $\geq 18$  years of age who underwent bariatric surgery (SG or RYGB) were included in the study (Fig. 1). SG and RYGB are the 2 most commonly performed operations at our institution. Patients who underwent adjustable gastric banding were excluded as this procedure represents a very low percentage of our overall bariatric case volume. Patients were stratified according to post-operative pain control medication use as follows: patients prescribed ketorolac in addition to opioids (ketorolac-opioid patients) vs. patients prescribed opioids alone (opioid-only patients). All data presented

includes patients with a hospital LOS  $\leq 7$  in order to exclude outliers.

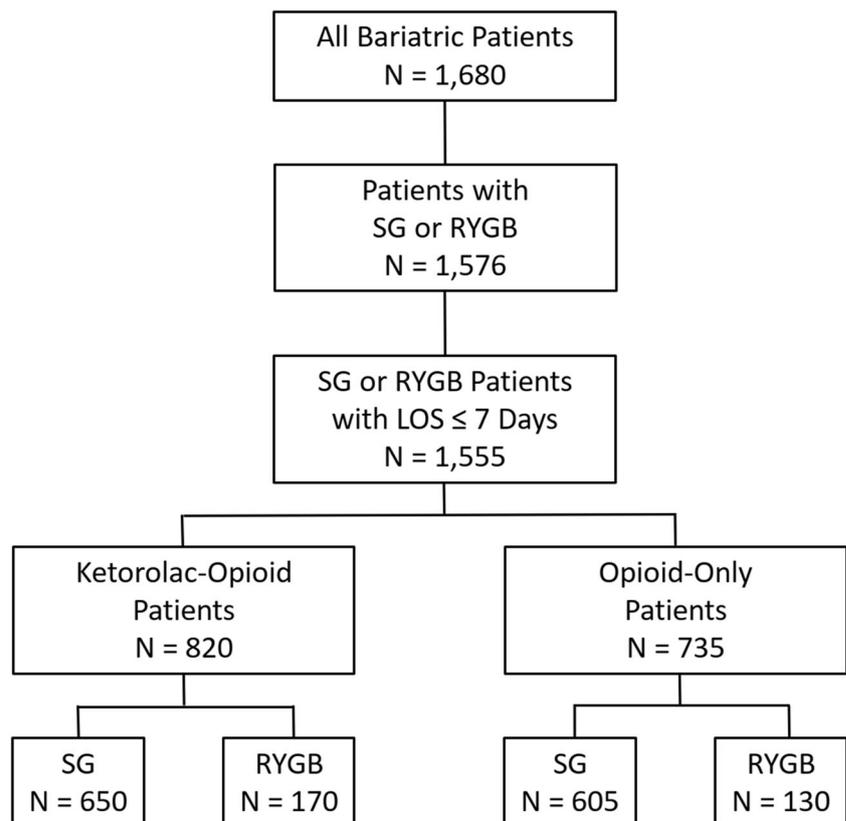
### Ketorolac and Opioid Use

The ketorolac and opioid use calculated in this study includes medications prescribed from the initiation of the procedure to discharge. Dosages are given as means  $\pm$  standard deviation (SD) in milligrams (mg). Opioid use includes morphine and the morphine equivalent, hydromorphone. Pre-operative opioid use was not abstracted. No other regional modalities, such as pain catheters, epidurals, liposomal bupivacaine, or transversus abdominis plane (TAP) blocks, were employed.

### Statistical Analysis

Data were presented as mean  $\pm$  SD for continuous covariates and percent for categorical variables. For the univariate group comparisons, the two-sample *t* test for continuous variables and the chi-squared tests or Fisher's exact test for categorical variables were used, as appropriate. A two-tailed significance level of 0.05 was used in all tests.

**Fig. 1** Flowchart of patient selection for study inclusion. Abbreviations: SG, sleeve Gastrectomy; RYGB, Roux-en-Y gastric bypass; LOS length of stay



## Results

### Demographics

Among the 1555 patients included in the study, 1184 patients (76.1%) were female and the overall average age was  $44.6 \pm 12.1$  years. Overall, the average pre-operative body mass index (BMI) was  $44.6 \pm 6.9$  kg/m<sup>2</sup> with an average pre-operative weight of  $121.7 \pm 24.5$  kg. Additionally, 1255 patients (80.7%) underwent SG while 300 (19.3%) underwent RYGB (Table 1).

### Hospital Length of Stay

There was a significant correlation observed between ketorolac use and LOS both following SG and RYGB (Table 2). On average, LOS was reduced by more than 13% for ketorolac-opioid patients compared to opioid-only patients.

### Ketorolac and Opioid Doses

The ketorolac-opioid patients were prescribed on average  $112.3 \pm 80.7$  mg of ketorolac for the entire period of hospitalization. The opioid requirements of patients in the ketorolac-opioid group were significantly less than opioid-only patients. On average, ketorolac-opioid patients were prescribed a total

of  $109.1 \pm 97.2$  mg of opioids for the entire inpatient hospitalization vs.  $167.9 \pm 85.2$  mg opioids for opioid-only patients ( $P < 0.001$ ). Accordingly, the average opioid consumption was reduced by more than 34% for ketorolac-opioid patients vs. opioid-only patients.

### Impact of Risk Factors on LOS

A further analysis into the potential confounders that could impact LOS revealed that RYGB and hypertension were associated with a longer LOS (Table 3). Sex, age, race, and the presence of diabetes, obstructive sleep apnea, and hyperlipidemia were not associated with a longer LOS.

### Post-operative Bleeding Rates

Clinically, significant post-operative bleeding was defined as bleeding requiring either a transfusion and/or reoperation. Among all patients, 18 (1.2%) had clinically significant post-operative bleeding. Ketorolac-opioid patients were not at an increased risk of post-operative bleeding vs. opioid-only patients ( $P = 0.097$ ). A comparison between patients with post-operative bleeding prescribed ketorolac-opioids vs. opioids alone is shown in Table 4. Furthermore, aside from age, there was no difference observed among the baseline parameters for patients with clinically significant bleeding compared to those without bleeding (Table 5). All Patients received

**Table 1** Baseline pre-operative characteristics of patients

Characteristics	All patients <i>N</i> = 1555	Ketorolac- opioid patients <i>n</i> = 820	Opioid-only patients <i>n</i> = 735	<i>P</i> value
Age (mean years $\pm$ SD)	41.3 $\pm$ 12.1	41.1 $\pm$ 12.0	41.6 $\pm$ 12.3	0.472
Sex ( <i>N</i> , %)				0.165
Female	1184 (76.1)	636 (77.7)	548 (74.6)	
Male	371 (23.9)	184 (22.3)	187 (25.4)	
BMI (mean kg/m <sup>2</sup> $\pm$ SD)	44.6 $\pm$ 6.9	44.0 $\pm$ 7.1	44.1 $\pm$ 6.8	0.723
Weight (mean kg $\pm$ SD)	121.7 $\pm$ 24.5	122.1 $\pm$ 25.2	121.4 $\pm$ 23.7	0.626
Surgery type ( <i>n</i> , %)				0.129
SG	1255 (80.7)	650 (79.3)	605 (82.3)	
RYGB	300 (19.3)	170 (20.7)	130 (17.7)	
Race ( <i>n</i> , %)				
White	906 (58.3)	437 (53.3)	469 (63.8)	<0.001
Black/African American	305 (19.6)	178 (21.7)	127 (17.3)	0.028
Unknown/not reported/other	344 (22.1)	205 (25.0)	139 (18.9)	0.004
Comorbidities ( <i>n</i> , %)				
T2D	349 (22.4)	177 (21.6)	172 (23.4)	0.391
OSA	396 (25.5)	205 (25.0)	191 (26.0)	0.655
HTN	636 (40.9)	326 (40.0)	310 (42.2)	0.332
HLD	297 (19.1)	158 (19.3)	139 (18.9)	0.858

BMI body mass index, SG sleeve gastrectomy, RYGB Roux-en-Y gastric bypass, T2D type II diabetes mellitus, OSA obstructive sleep apnea, HTN hypertension, HLD hyperlipidemia, na not applicable, SD standard deviation

**Table 2** Comparison of LOS between ketorolac-opioid patients vs. opioid-only patients

Length of stay	Ketorolac-opioid patients <i>n</i> = 820	Opioid-only patients <i>n</i> = 735	<i>P</i> value
LOS-SG (mean days ± SD)	1.7 ± 0.9	2.0 ± 0.9	< 0.001
LOS-RYGB (mean days ± SD)	2.1 ± 0.7	2.4 ± 0.8	0.005
LOS-total(mean days ± SD)	1.8 ± 0.9	2.1 ± 0.9	< 0.001

*LOS* length of stay, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *na* not applicable, *SD* standard deviation

5000 units heparin subcutaneous pre-operatively and received heparin subcutaneous every 8 h postoperatively. The most common source of bleeding was intra-abdominal bleeding along the staple line.

### Discussion

Our study demonstrates that post-operative ketorolac use as an opioid adjunct after bariatric surgery not only reduces opioid

consumption and LOS, but more importantly, is not associated with an increased risk of post-operative bleeding requiring transfusion or reoperation. These findings are clinically relevant, as a decrease in opioid use may aid in the avoidance of a myriad of associated problematic side effects, which in turn could help to avoid post-operative respiratory complications and contribute to shorter LOS [2]. Furthermore, a potential benefit of a shorter LOS may be a decrease in the occurrence of nosocomial infections [16]. The use of NSAIDs in a

**Table 3** Impact of patient characteristics on LOS

Characteristics	LOS (mean days ± SD)	<i>P</i> value
Age		0.056
< 45 years	1.9 ± 0.9	
≥ 45 years	2.0 ± 0.8	
Sex		0.630
Female	2.0 ± 0.9	
Male	1.9 ± 1.0	
Surgery type		< 0.001
SG	1.9 ± 0.9	
RYGB	2.3 ± 0.8	
Race		0.573
White	1.9 ± 0.7	
Black/African American	2.0 ± 0.9	
Unknown/not reported/other	2.0 ± 0.9	
T2D		0.060
Yes	2.0 ± 0.9	
No	1.9 ± 0.9	
OSA		0.116
Yes	2.0 ± 1.0	
No	1.9 ± 0.8	
HTN		0.001
Yes	2.0 ± 0.9	
No	1.9 ± 0.9	
HLD		0.188
Yes	2.0 ± 0.9	
No	1.9 ± 0.9	

*SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *T2D* type II diabetes mellitus, *OSA* obstructive sleep apnea, *HTN* hypertension, *HLD* hyperlipidemia, *LOS* length of stay, *na* not applicable, *SD* standard deviation

**Table 4** Comparison of patients with clinically significant post-operative bleeding

Characteristics	Ketorolac-opioid patients post-operative bleeding <i>n</i> = 6	Opioid-only patients post-operative bleeding <i>n</i> = 12	<i>P</i> value
Age (mean years ± SD)	50.4 ± 17.2	44.7 ± 10.8	0.484
Sex ( <i>n</i> , %)			0.288
Male	1 (16.7)	5 (41.7)	
Female	5 (83.3)	7 (58.3)	
BMI (mean kg/m <sup>2</sup> ± SD)	43.3 ± 6.8	43.8 ± 6.5	0.891
Weight (mean kg ± SD)	114.6 ± 13.7	126.1 ± 23.7	0.215
Surgery type ( <i>n</i> , %)			0.180
SG	4 (66.7)	11 (91.7)	
RYGB	2 (33.3)	1 (8.3)	
Pre-operative aspirin use ( <i>n</i> , %)	1 (16.6)	2 (16.6)	1.000
Mean operative time for index case (hours ± SD)	2.0 ± 0.5	2.0 ± 0.6	0.840
DVT chemoprophylaxis for index case ( <i>n</i> , %)			0.737
Heparin	3 (50.0)	5 (41.7)	
Enoxaparin (Lovenox)	3 (50.0)	7 (58.3)	
EBL for index case (mean ml ± SD)	25.0 ± 3.2	37.5 ± 23.8	0.093
Post-operative transfusion ( <i>n</i> , %)	5 (83.3)	8 (66.7)	0.457
Mean no. of blood units transfused ± SD	2.0 ± 0.8	3.2 ± 2.0	0.083
Reoperation for bleeding ( <i>n</i> , %)	2 (33.3)	7 (58.3)	0.317

*BMI* body mass index, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *LOS* length of stay, *DVT* deep venous thrombosis, *EBL* estimated blood loss; *no.* number, *ml* milliliters, *na* not applicable, *SD* standard deviation

**Table 5** Comparison of baseline characteristics for patients with and without clinically significant post-operative bleeding

Characteristics	Patients with post-op bleeding <i>n</i> = 18	Patients without post-op bleeding <i>n</i> = 1537	<i>P</i> value
Age (mean years $\pm$ SD)	47.9 $\pm$ 12.1.1	41.2 $\pm$ 12.1	0.039
Sex ( <i>n</i> , %)			0.342
Male	6 (33.3)	365 (23.7)	
Female	12 (66.7)	1172 (76.3)	
BMI (mean kg/m <sup>2</sup> $\pm$ SD)	43.6 $\pm$ 6.6	44.1 $\pm$ 7.0	0.793
Weight (mean kg $\pm$ SD)	122.0 $\pm$ 21.8	122.0 $\pm$ 24.6	0.971
Surgery type ( <i>n</i> , %)			0.776
SG	15 (83.3)	1240 (80.7)	
RYGB	3 (16.7)	297 (19.3)	
Race ( <i>n</i> , %)			
White	12 (66.7)	894 (58.2)	0.467
Black/African American	5 (27.8)	300 (19.5)	0.380
Unknown/not reported/other	1 (5.5)	343 (22.3)	0.088

*BMI* body mass index, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *na* not applicable, *SD* standard deviation

multimodal analgesia regimen is recommended as part of the Enhanced Recovery After Surgery (ERAS) protocols across many surgical specialties, including general, colorectal, and orthopedics surgery, due to its multiple benefits [17–19]. In our institution, ketorolac is used in a standardized bariatric surgery ERAS protocol which typically involves an intra-operative dose given at the end of the index procedure as well as scheduled post-operative dosing (15 or 30 mg intravenous [IV] or intramuscular [IM] every 6 h, up to 120 mg/day; with per os [PO] continuation if necessary, up to 40 mg/day).

There are limited studies that evaluate the use of ketorolac in the bariatric surgical setting. For example, Govindarajan et al. found that perioperative use of ketorolac resulted in a more stable intra-operative environment with regard to blood pressure and pulse rate, a lower post-operative pain score, and improved outcomes in nausea and vomiting, hypotension, and respiratory depression after laparoscopic RYGB surgery [20]. In contrast, the benefits of ketorolac have been more consistently reported in other surgical sub-specialties, including colorectal, pediatrics, orthopedics, plastic surgery, and spinal surgery [4–10]. For example, in an evaluation of post-operative pain management, Garimella et al. demonstrated that ketorolac reduced opioid consumption by 25–45% among colorectal surgery patients [5]. In a systematic review of patients undergoing major surgery, Marret et al. showed that replacing opioids with NSAIDs decreased the incidence of post-operative nausea, vomiting, and sedation; patients treated with NSAIDs also showed a reduced trend, albeit not statistically significant, in opioid adverse side effects in the post-operative setting including pruritus, urinary retention, and respiratory depression [3]. Ebersson et al. also found a significant reduction in total opioid consumption in pediatric orthopedic patients with and without post-operative ketorolac use at 2.29

$\pm$  3.98 mg vs. 10.02  $\pm$  3.39 mg ( $P < 0.05$ ), respectively; additionally, patients who received ketorolac had a significantly shorter LOS at 3.63  $\pm$  1.64 days vs. non-ketorolac patients at 4.74  $\pm$  1.76 days ( $P < 0.05$ ) [4].

Prolonged LOS could have a negative impact on patient outcomes by increasing the risk of acquiring nosocomial infections. Employing a database of all admitted patients to hospitals in a single state during a 1-year period, Hassan et al. demonstrated that LOS and the probability of developing an infection are interdependent: a 1-day increase in LOS resulted in 1.37-fold higher risk of acquiring a nosocomial infection. The authors, in turn, indicated that nosocomial infection then further increased the average LOS by an additional 9.32 days [16].

In addition to prolonged LOS, bleeding is another clinically relevant problem associated with ketorolac use and is particularly germane to bariatric surgery given the frequent use of stapling devices. Anecdotally, some surgeons are reluctant to use ketorolac due to concerns for increased risk of bleeding; however, we observed that ketorolac was not associated with an increase in clinically significant post-operative bleeding. Furthermore, a meta-analysis by Strom et al. compared patients on ketorolac vs. opioids and revealed that the overall association between ketorolac and gastrointestinal bleeding was small when used for  $\leq 5$  days (odds ratio [OR] = 1.17; 95% confidence interval [CI], 0.99 to 1.30) [21]. A more recent meta-analysis by Gobble et al. analyzed 27 studies and demonstrated that post-operative bleeding occurred in 33 out of 1304 patients (2.5%) in the ketorolac group vs. 21 out of 1010 (2.1%) in the control group (i.e., non-ketorolac patients using morphine, placebo) (OR, 1.1; 95% CI, 0.61 to 2.06;  $P = 0.72$ ) [22]. In addition, a subset of studies in Gobble et al.'s meta-analysis reported no clinically significant impact

on bleeding time for patients who received ketorolac. Another study by Greer et al. analyzed the effect of ketorolac alone and in combination with low-dose heparin on hemostasis on 12 healthy male subjects in a double-blinded crossover study. They concluded that the modest prolongation of bleeding time associated with ketorolac use due to platelet inhibition is unlikely to be of major clinical significance, as the value still remains within the normal range in the majority of subjects, and that the effect of ketorolac was comparable to that of aspirin. Furthermore, they found no interaction between ketorolac and heparin [23].

There are some important limitations to this study that should be highlighted. First, this is a retrospective study. Second, the findings in our study are from a tertiary center and may be unique to our patient population. Larger multi-center studies in bariatric surgery are necessary to better evaluate the post-operative risks and benefits of ketorolac use. Third, while we performed a detailed analysis of the bariatric surgery patients with post-operative bleeding in ketorolac-opioid vs. opioid-only groups, we did not perform the same detailed analysis in patients with and without clinically significant post-operative bleeding for the entire cohort. Finally, the results of this study relate only to the effects of ketorolac on bleeding, as that is the most important concern; other side effects, such as gastric or marginal ulcer, or leaks, were not studied. We are hopeful that a future multi-center prospective study would help to address these issues.

## Conclusion

In our study, bariatric surgery patients prescribed ketorolac as an adjunct to opioids had significantly lower post-operative opioid consumption and shorter LOS compared to opioid-only patients. More importantly, ketorolac use did not adversely impact clinically significant post-operative bleeding rates. To the best of our knowledge, this study represents the largest assessment of ketorolac use in bariatric surgery. Future studies in the bariatric surgery setting should further evaluate the benefits of ketorolac use not only for decreasing LOS and opioid consumption but also the impact on improving patient satisfaction and the feasibility of completely removing opioids from post-operative pain management protocols.

## Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

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